UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/447,681	11/23/99	ROTH J	INRP.003--2/

HM22/0814

GINA N SHISHIMA ESQ
ARNOLD WHITE & DURKEE
750 BERING DRIVE
HOUSTON TX 77057-2198

EXAMINER	
CROUCH, D	
ART UNIT	**PAPER NUMBER**
1632	3

DATE MAILED: 08/14/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/447,681	Roth
Examiner	**Group Art Unit**
Deborah Crouch	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *66-85* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *66-85* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 72-85 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-26, 28-32, 34-36, 38-44, 46-57, 61-66, and 68-123 of copending Application No. 08/224,232. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 72-85 encompass and are obvious over claims 22-26, 28-32, 34-36, 38-44, 46-57, 61-66, and 68-123 of '232. The instant specification defines the adenovirus vector comprising a wild type p53 gene as preferentially lacking a functional E1B gene. Thus, at the time of the instant invention it would have been obvious to the ordinary artisan to treat a cancer cells as claimed given the claims in '232. Applicant is reminded that the specification is available to define the terms of the claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 66-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification does not contemplate adenoviral vectors comprising a wild type p53 gene operably linked to a promoter, the specific embodiments where the promoter is a CMV, RSV, β-actin or SV40 promoter, or methods of treating a cancer cell in a patient comprising introducing to the cell an adenovirus vector comprising a wild type p53 gene under the control of a promoter, or the specific embodiments of a CMV promoter. The examiner has read and re-read the specification in its entirety and in particular to the citations of support on page 4 of the preliminary amendment filed November 11, 1999. At page 7, lines 1-7, discusses the evidence in the art that mutations of the p53 gene cause lung cancer; page 9, line 6-8, states that the vector construct for introducing a wild type p53 gene under the control of a β-actin promoter is a retroviral vector; page 9, lines 14-15, states wild type p53 constructs; page 14, lines 26-27 and 31-34, discusses antisense RNA expressed from any promoter; page 15, lines 1-5, state that the β-actin, RSV, SV40 and a CMV promoters are used to express antisense RNA; page 25, lines 4-5, discuses that mutations of a p53 gene are the most frequently found mutations in human cancers; page 26, lines 13-16, states that the inventors feel that the reversal of a single altered genetic event in a cancer cells can potential reverse critical features of the malignant phenotype; page 27, lines 24-28, states that the protocol focuses on the regional delivery of wild type p53 for the treatment of tumors; page 33, lines 9-11, states that adenovirus can be used to introduce an antisense intron; and page 66, lines 10-18, states that tumors should be resected and that to the residual tumor the appropriate retroviral vector is to be injected. Further, the examiner has found at page 63, lines 30-34, it is stated that antisense p53 in a retrovirus is used; page 64, lines 27-31, states a retroviral construct comprising p53 cDNA; page 65, lines 7-22, states retrovirus mediated transfer of p53 cDNA and pages 67, line 15 to page 68, line 1, states risks of retroviruses. At no place in the specification is the invention of the claims clearly set forth so that the reader would realize that which applicant perceived as their invention at the time of filing. In the places where adenovirus or the specific classes of promoters claimed are disclosed, each such disclosure is within

the context of antisense RNA production. Therefore the specification lacks a written description of the invention as claimed.

Claims 72-85 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide guidance as to those adenoviral vectors which contain and express a p53 gene where the gene is operably linked to a promoter, such as the CMV, RSV, β-actin or SV40 promoter, such that the level of expression obtained would be effective in causing an effective treatment for the target cancer cell. It is noted that the specification only discloses the methods claimed as being useful to cause an inhibition of tumor growth. At the time of filing the art as a whole taught that gene therapy was unpredictable. While the level of skill in the art of gene transfer was high at the time of filing, gene therapy remained very unpredictable. Marshall states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (p. 1050, col. 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (p. 1054, col. 3). James Wilson, one skilled in the art, saying that " '{the actual vectors - how we're going to practice our trade - haven't been discovered yet" (p. 1055, col. 2). Culver et al. , reviewing gene therapy for cancer, conclude that the "primary factor hampering the widespread application of gene therapy to human disease is the lack of an efficient method for delivering genes *in situ*, and developing strategies to deliver genes to a sufficient number of tumor cells to induce complete tumor regression or restore genetic health remains a challenge" (p. 178). Hodgson discusses the drawbacks of viral transduction and chemical transfection methods, and states that " {developing the techniques used in animal models, for therapeutic use in somatic cells, has not been straightforward" (pp. 459-460). Miller et al. also review the types of vectors available for *in vivo* gene therapy, and conclude that " for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances... targeting strategies outlined in this review, which are currently only at the

experimental level, will have to be translated into components of safe and highly efficient delivery systems" (p. 198, col.1). Furthermore, Gutierrez et al. reviews this technology, and indicates at pages 716-717 that there were two major limitations to mammalian cell transfection. The first is a much lower efficiency of gene expression in comparison with prokaryotic systems, with considerable differences between eukaryotic cell lines. Unlike rodent cells, most primate and human cells can integrate only a small amount of foreign DNA (about 6 kilobases); as a result, only about 10-30% of clones selected for the expression of one transcription unit will also contain a second unit in intact form. The second problem is the short lived response after successful transfection (a few months at most) regardless of the method used. We know very little about the processing steps within the cell. Clearly, there are problems of degradation by extracellular nucleases, absorption onto and uptake into cells, transport from cytoplasm to nucleus integration into host chromosomes, mutation, the expression of non-integrated DNA, and the transcriptional control of the transgene. Without guidance in the specification of adenoviral vectors, promoters, routes of delivery and delivery routes, the skilled artisan would have needed to engage in an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

Furthermore, the instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genetech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). It is argued that instantly claimed invention, when examined in view of the state of the art at the time of filing and the disclosure, is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 67-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of these claims state "the XXX promoter". However, there are several varieties of these promoters known in the art. It is not clear to which specific promoter applicant means, and thus the metes and bounds of the claims are clear. Applicant should consider claiming "a XXX promoter".

This application has been given priority to October 29, 1993, the filing date of 08/145,826. Those applications with earlier filling dates to which applicant claims priority do not provide an enabling disclosure of adenovirus vectors comprising a p53 gene or the treatment of tumors by administering such a vector.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 66-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (1990) Science 250, 1576-1579 in view of Wilkinson et al (1992) Nucleic Acids Res. 20, 2233-2239, Colicos et al (1991) Carcinogenesis 12, 249-255, Rajan et al (1991) J. Virol. 65, 6553-6561 and Hitt et al (1990) Virol. 179, 667-678.

Claims 66-71 are drawn to adenovirus vectors comprising a wild type p53 gene or a human wild type p53 gene under the control of a promoter, where the promoter can be a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter.

Chen et al teach retroviral vectors comprising a wild type human p53 operably linked to the retroviral LTR (page 1576, col. 3, Figure 1). Chen et al teach that wild type 53 is expressed in transduced

Saos cells, and that the transduced cells failed to form colonies on soft agar or tumors in nude mice (page 1577, col. 2, line 12 to col. 3, line 8). Chen et al also teach that wild type p53 counters the transformation phenotype conferred by a mutant p53 when both genes are present in equal gene dosage (page 1579, col. 1, parag. 1 to col. 2, line 1 and col. 2, parag. 1, lines 25-28). Chen et al do not teach adenoviral vectors comprised of a wild type p53 gene under the control of a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter. Wilkinson et al teach the production of an adenovirus expression system where a CMV promoter regulates expression of lacZ (page 2234, col. 1, parag. 5, lines 1-3). Wilkinson et al also teach that the adenovirus-CMV system can be used to studies of gene expression and gene regulation (page 2238, col. 2, parag. 4, lines 1-4). Colicos et al teach an adenovirus vector comprising a T4 *denV* gene operably linked to the RSV promoter, the RSV LTR (page 250, col. 1, parags. 4-7, figure 1 and figure 2). The vector, Ad5denV, was shown to partially complement the excision repair deficiency in primary fibroblasts from xeroderma pigmentosa patients (page 254, col. 1, parag. 2, and page 253, figures 6 and 7, and Table 1). Rajan et al teach an adenoviral vector comprising a cDNA sequence encoding an SV 40 small-t antigen operably linked to an SV40 promoter (page 6554, col. 1, parag. 2). Rajan et al teach that the expression of the SV40 small-t antigen results in the transactivation of adenovirus EII early promoter (page 6557, col. 1, line 13 to col. 2, line 4). Hitt et al teach an adenovirus where the expression of the E1A gene is regulated by a human β-actin promoter (page 670, col. 1, line 12 to col. 2, line 2, and figure 1). Hitt et al teach that E1A production is 3 to 5 times higher than by wild type adenovirus (page 675, col. 2, parag. 1, lines 11-16). Thus it would have been obvious to the ordinary artisan at the time of the instant invention to determine the reversal of a transformed phenotype by expressing in an adenoviral vector comprising a human wild type p53 gene operably linked to a promoter, and specifically where the promoter is a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter, given the teachings of Chen et al that wild type p53 can reverse the transformed phenotype of tumor cells when the cells are transduced with a retroviral vector comprising a human wild type p53 gene operably linked to a promoter in view of the teachings of Wilkinson et al, Colicos, Rajan et al or Hitt et al that a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter functions within a

adenovirus to regulate expression of a sequence encoding a protein of interest. All that is required that there is a reasonable expectation of success and motivation to make the claimed adenovirus vectors. Motivation is provided by Chen et al in stating that expression of p53 in cells Saos cells which lack functional p53 reverts the transformed phenotype, and that such suggests possible clinical use of p53 gene replacement (page 1579, col. 1, parag. 1, line 1 to col. 2, line 1 and col. 2, lines 21-25).

Claims 72-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,532,220 issued July 2, 1996 (Lee) in view of Wilkinson et al (1992) Nucleic Acids Res. 20, 2233-2239.

Lee teaches methods of treating cancer cells, and specifically lung cancer cells, by introducing a retroviral vectors comprising wild type p53 gene operably linked to the LTR (col. 2, lines 23-25, col. 6, lines 2-4 and claims 1-6). Saos cells transduced with the retroviral vector failed to develop tumors when injected into nude mice (col. 8, Table 2, and col. 8, line 67 to col. 9, line 5). However, Lee does not teach the treatment of cancer cells by administering an adenoviral vector comprising a p53 gene operably linked to a promoter. Wilkinson et al teach the production of an adenovirus expression system where a CMV promoter regulates expression of lacZ (page 2234, col. 1, parag. 5, lines 1-3). Wilkinson et al also teach that the adenovirus-CMV system can be used to studies of gene expression and gene regulation (page 2238, col. 2, parag. 4, lines 1-4). Thus, at the time of filing, it would have been obvious to the ordinary artisan to treat cancer cells in a patient given the teaches of Lee that supplying the p53 gene to cancer cells alters their ability to induce tumor growth in nude mice in view of the teachings that adenoviral vectors comprising a promoter operably linked to a DNA sequence encoding a protein of interest provide for delivery of the protein to the target cells as found, and that the Ad-CMV construct is useful in studying gene expression and regulation in Wilkinson et al. Further, given the specific claim of lung cancer cell, the particular type of lung cancer cell would have been obvious at the time of filing, as would have been the treatment of a human cell having a p53 mutation. Tumor resection prior to treatment was well known within the art at the time of filing, and within the scope of skills of the ordinary artisan at the time of filing. The determination of the specific route of delivery for the vector is routine experimentation to optimize the method, which is to the introduction of an adenoviral vector comprising wild type p53 operably linked to a

promoter without an effect resulting from the method. The claims merely state "a method of treating" which implies at a minimal no effect on the target tumor. For example, if one takes aspirin for a headache, one has treated the headache, but the aspirin may not relieve any symptom associated with headache. The same is true for the instant claims. The cited prior art provides sufficient motivation and teachings for inserting an adenovirus comprising a p53 gene operably linked to a promoter into a tumor cell in a patient. Routine experimentation is permitted within the confines of 35 U.S.C. 103, and in this situation, the routine experimentation only needs to be for delivery. Applicant may wish to consider amending the claims to state an effect of the method on the target tumor cell or target tumor.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

The fax number is (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Dr. D. Crouch
August 10, 2000